

PPAR γ Agonists Pioglitazone and Rosiglitazone Prevent Renal Tissue Damage in Hypothyroid Rats

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Running title: Effect of PPAR- γ agonists on :PTU-caused renal tissue damage

Abstract

Background: There is a relationship between thyroid function status and kidney function. In this study the effect of PPAR- γ agonists, pioglitazone and rosiglitazone, on renal tissue damage caused by hypothyroidism was evaluated.

Methodes: The groups were including: 1- control, the rats received drinking water, 2- Propylthiouracil (PTU), the animals received drinking water containing PTU (0.05%), 3- PTU+ pioglitazone (Pio)10, 4- PTU+Pio20, 5- PTU+ rosiglitazone (Rosi), 2 and 6- PTU+ Rosi 4. Besides PTU, the animals in 4 recent groups received 10 or 20 mg/kg of pioglitazone, or 2 or 4 mg/kg of rosiglitazone (i.p.) respectively. After anesthetizing, the blood samples of the animals were collected to assess the serum level of BUN and creatinine. Then their kidney tissue was prepared to measure malondialdehyde (MDA), total thiol groups, superoxide dismutase (SOD) and catalase (CAT).

Results: PTU enhanced serum level of blood BUN and creatinine ($P<0.001$). PTU also increased MDA concentration and decreased the level of total thiol and SOD and CAT activity ($P<0.001$). Pioglitazone and rosiglitazone attenuated all the effects of PTU ($P<0.05$, $P<0.01$ and $P<0.001$).

Conclusion: Based on results, pioglitazone and rosiglitazone could improve detrimental effects of hypothyroidism on kidney function through balancing oxidative stress status.

Keywords: Hypothyroidism, Kidney, PPAR γ , Pioglitazone, Rosiglitazone

Introduction

Kidney diseases affect a large number of individuals in the world.¹ Some drugs,² high blood pressure³ and diabetes⁴ have been considered as risk factors causing kidney diseases. Chronic kidney disease (CKD) is a progressive ailment with high mortality that happens mostly in elderly people with hypertension and diabetes. Increased prevalence of CKD has been reported in a large number of studies.⁵

The results of previous studies indicate that there is a near relationship between thyroid gland function status and kidney function.⁶ Researchers reported that hypothyroidism can disturb the kidney function by change of renal hemodynamic and glomerular structure.⁷ CKD associated with

hypothyroidism has been also reported in human studies. Clinical studies reveal that prevalence of primary hypothyroidism is roughly %18 among patients with CKD.⁸ In patients with CKD also impairment of thyroid hormones metabolism has been reported.⁹ In addition, inflammatory reactions and oxidative stress have been proposed to have a basic role in development of kidney diseases such as diabetic nephropathy.¹⁰ Hypothyroidism can lead to the over generation of inflammatory cytokines¹¹ and oxidative stress.¹² In a rat model of propylthiouracil (PTU)- induced hypothyroidism, increase of oxidant paraments such as malondialdehyde (MDA) and decrease of antioxidant factors such as thiol, superoxidase dismutase (SOD) and catalase (CAT) led to kidney dysfunction.¹³ Methimazole - induced hypothyroidism also enhanced the reactive oxygen species (ROS) and reduced SOD and catalase activity and lastly attenuated the normal function of kidney in rats.¹⁴ In hypothyroid rats by carbimazole, increased level of inflammatory cytokines including TNF- α and IL-6 resulted in the renal damage.¹⁵

Peroxisome proliferator activated receptor gamma (PPAR γ) is a ligand – stimulated nuclear receptor that has an important role in normal function of kidney.¹⁶ PPAR γ ligands have been suggested to involve in regulation of lipids and glucose metabolism, and improvement of insulin sensitivity.¹⁷ The protective role of PPAR γ agonists against oxidative stress damage has also been confirmed. The activation of PPAR γ can up-regulate the antioxidant indicators including superoxide dismutase (SOD) and glutathione peroxidase and down-regulate the production of oxidant factor such as nitric oxide (NO).^{18,19} Pioglitazone and rosiglitazone are two PPAR γ agonists which have a high affinity to PPAR γ receptor.²⁰ In hypothyroid rats by PTU, administration of pioglitazone and rosiglitazone for 6 weeks reversed the detrimental effects of PTU on liver tissue through decreasing the MDA level and increasing the thiol concentration and the SOD and CAT activity.²¹ Considering these evidence, this study aims to investigate whether

PPAR- γ agonists, pioglitazone and rosiglitazone, can improve the hypothyroidism-induced kidney injury by balancing oxidative stress status.

Materials and methods

Male Wistar rats (total = 42) were grouped into six groups and each group was including 7 rats.

G power software and two variables including MDA concentration as an oxidative stress indicator and BUN as a marker of kidney function were considered to calculate sample size. Considering $\alpha = 0.05$, power = 0.95, and using the mean of MDA (minimum = 13, maximum = 36 and, and SD = 9), and the mean of BUN (minimum = 29, maximum = 50, and SD = 9) from previous studies^{16,22}, the sample size was calculated to be 42.

The groups were as follows: control, Propylthiouracil (PTU), PTU- pioglitazone (Pio)10, PTU+ Pio20, PTU+ rosiglitazone (Rosi)2 and PTU+Rosi4. The rats of control group received water. Animals of the rest groups received 0.05% PTU dissolved in water. In PTU+Pio10 and PTU+Pio20 groups, the animals also were daily received 10 and 20 mg/kg of pioglitazone respectively. In PTU+Rosi2 and PTU+Rosi4 groups, the rats were treated by 2 and 4 mg/kg of rosiglitazone respectively.²¹ Both pioglitazone and rosiglitazone were dissolved in and then diluted by saline diluted dimethyl sulfoxide (DMSO) (final concentration 3%) and injected intraperitoneally. The rats of control and PTU groups received ip injection of saline diluted DMSO instead of pioglitazone and rosiglitazone. Induction of hypothyroidism by PTU and treatment with pioglitazone and rosiglitazone were carried out simultaneously. Rats were housed in standard conditions ($22 \pm 2^\circ\text{C}$ temperature, 12 h light/dark cycle, and %30 -%60 humidity). In addition, the animals were free to access the food. In throughout project, the guideline for working with experimental animals was confirmed by ethical committee of Mashhad university of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.304). After 6 weeks treatment,²¹ the fasting animals

were anesthetized at 8 am deeply by urethan and the serum samples were collected for determination of blood urea nitrogen (BUN) and creatinine concentration. After collecting the samples, the animals were euthanized by urethan. Finally, the kidney tissue was separated for evaluation of oxidative stress status.

Assessment of BUN and creatinine: To estimate the blood concentration of BUN and creatinine, the colorimetric kits (Pars Azmoon Company, Tehran, Iran) were used. Assessment was accomplished based on the instruction of kits.

Measurement of MDA: To measure the MDA level in kidney tissue, the spectrophotometric method was fulfilled. 1 mL of the kidney homogenates and 2 mL of TBA/trichloroacetic acid (TCA)/hydrochloric acid (HCL) were mixed. The mixture was heated by water bath for 40 minutes. Then, the solution was centrifuged and absorbance was recorded at 535 nm. In the end, MDA concentration was collected and expressed as nmol/g tissue.²³

Determination of total thiol content: DTNB (2, 2'-dinitro-5, 5'-dithiodibenzoic acid) as a reagent was used for the determination of thiol. In the first, 5 mL of the tissue homogenate was combined with 1 mL Tris-EDTA buffer and the absorbance was read at 412 nm. Then, 20 μ L of DTNB was mixed with prior solution, and was incubated in room temperature for 15 min. The absorbance was measured at 412 nm again.²²

Estimation of SOD activity: SOD activity was assessed by determining its capability in inhibition of auto-oxidation of pyrogallol. The kidney tissue homogenate was centrifuged for 15 min. Supernatant was mixed with 1 mL of pyrogallol (0.6 mM), 15 mL of Tris-HCl buffer (pH=8.2) and 0.5 mL of EDTA (6 mM). Then, the rate of auto-oxidation of pyrogallol was recorded at 570 nm by a spectrophotometer.²²

Estimation of CAT activity: CAT activity was measured by Aebi method. In this method, H₂O₂ (30 mM) was used as substrate. Decline in absorbance at 240 nm was considered as index of CAT activity.²²

Statistical analysis

Findings of study were exhibited as means $\pm$ SEM. One- way ANOVA followed by Tukey's test were employed to compare the results of groups and differences with $P < 0.05$ was statistically significant.

Results

Renal function markers

The results of blood concentration of BUN indicated higher level of this compound in PTU group than control group ($P < 0.001$). Administration of the higher dose of pioglitazone attenuated the enhancing effect of PTU on BUN concentration in PTU-Pio20 group compared with PTU group ($P < 0.01$), but there was no significant difference between PTU-Pio10 and PTU group. The results of injection of rosiglitazone also declared that the level of BUN was lower in both PTU-Rosi2 and PTU-Rosi4 groups versus PTU group ($P < 0.05$ and $P < 0.001$ respectively). According to the results, the serum level of BUN in PTU-Rosi4 group was lower than PTU-Pio10 group ($P < 0.05$) and PTU-Rosi2 group ($P < 0.001$) (Figure 1A).

The results also showed that the rats of PTU group had a high blood concentration of creatinine than those of control group ($P < 0.001$). Based on findings, the level of creatinine in the rats of PTU-Pio20 group reduced when it was compared with PTU group ($P < 0.001$), but there was no significant difference between PTU-Pio10 and PTU groups. It was also detected that the level of this kidney index significantly decremented in PTU-Rosi4 compared with PTU group ($P < 0.001$). We did not observe no significant difference between PTU-Rosi2 group and PTU group. There

was a significant difference in serum level of creatinine between PTU-Rosi4 group and PTU-Pio10 groups ($P<0.05$ and $P<0.01$ respectively) (Figure 1B).

Oxidative stress markers

According to the results, the exposed rats to PTU had higher level of MDA concentration and lower concentration of total thiol in kidney tissue compared with control group ($P<0.001$ for both) (Figure 3). The use of pioglitazone (20 mg/kg) resulted in a noticeable reduction in MDA concentration in the kidney tissue of PTU-Pio20 group versus PTU group ($P<0.01$), but there was no significant difference between PTU-Pio10 group and PTU group. The results also revealed that MDA concentration in the kidney tissue of PTU-Rosi4 group was lower than PTU group ($P<0.001$). MDA level in the kidney tissue of PTU-Rosi4 group was lower than PTU-Pio 10, PTU-Pio 20 and PTU-Rosi2 groups ($P<0.0001$ and $P<0.001$) (Figure 2A).

The total thiol level in PTU-Pio20, PTU-Rosi2 and PTU-Rosi4 groups was higher than PTU group ($P<0.001$ for all). The total thiol concentration in kidney tissue of PTU-Rosi4 group was higher than PTU-Rosi2, PTU-Pio10 and PTU-Pio20 groups ($P<0.001$ for all) (Figure 2B).

Antioxidant enzymes

According to the biochemical results, the PTU exposed rats had lower SOD and CAT activity in kidney tissue compared with control group ($P<0.001$ for both) (Figure 4A and B). Administration of 20 mg/ kg pioglitazone and also both doses of rosiglitazone improved SOD activity in the kidney tissue of PTU-Pio 20, PTU-Rosi2 and PTU-Rosi4 groups compared with the PTU group ($P<0.01$ - $P<0.001$). The SOD activity of PTU-Rosi4 group was higher than PTU-Pio1 and PTU-Pio20 groups ($P<0.005$ and $P<0.01$) (Figure 3A).

The activity of CAT in PTU-Rosi2 and PTU-Rosi4 groups was higher than PTU group ($P < 0.01$ and $P < 0.0001$). In addition, CAT activity of PTU-Rosi4 group was higher than PTU-Pio10 and PTU-Rosi2 groups ($P < 0.001$) (Figure 3B).

Discussion

Hypothyroidism is a condition in which thyroid gland is unable to synthesize enough thyroid hormones.²⁴ Hypothyroidism is characterized by symptoms including depression, drowsiness, disability in cold tolerance, and bradycardia.²⁵ Induction of hypothyroidism by adding 0.05% of PTU to drinking water of rats is a common route and widely is used by researchers.²⁶ In this study also, hypothyroidism is induced by adding 0.05% of PTU to drinking water of rats. The results of previous studies also showed that PTU induced hypothyroidism and mitigated the serum level of T4.^{21,27}

Growing reports show that the change in thyroid gland status seriously can affect kidney function.^{28,29} Hypothyroidism has been suggested to disturb the structure and function of kidneys in different periods of the life. The results of animal studies demonstrated that hypothyroidism reduced the renal blood flow, GFR and kidney weight.⁶ High blood concentration of uremic toxins resulting from CKD associated with hypothyroidism has been also reported.³⁰ Based on the results of our study, the PTU-induced hypothyroidism also impaired the kidney function in rats. This claim is confirmed via the increased level of BUN and creatinine in PTU group vis-à-vis control group.

It has been reported that impairment of thyroid gland function can imbalance oxidative stress status in different organs of the body.²⁷ Reduction of glutathione level and overproduction of oxidant factors have been linked to hypothyroidism.³¹ In individuals with subclinical and advanced

hypothyroidism, over generation of oxidant agents has also been detected.³² In the other hand, oxidative stress has been proposed as a basic cause in kidney dysfunction.³³ For instance, kidney damage resulting from high accumulation of free radicals in rat model of ischemia/reperfusion has been presented.³⁴ Excessive production of nitric oxide (NO) followed by over expression of inducible nitric oxide synthase (iNOS) is also considered as an important player in tubular injury.³⁵ Scientific evidence also show that modulation of oxidative stress condition by compounds with antioxidant properties can be useful in amelioration of kidney function.³⁶ In one study, researchers reported that dehydroepiandrosterone as a steroid compound with antioxidant effects could ameliorate the renal damages followed by oxidative stress in ischemia/reperfusion model in rats. In this research increased concentration of MDA and decreased total thiol level and CAT and SOD activity take placed in PTU group versus control group.³⁷

Activation of peroxisome proliferator activated receptor γ (PPAR γ) can induce a wide spectrum of biological functions such as adjustment of adipocytes differentiation, alignment of lipids and glucose metabolism, and improvement of immune system function.³⁰ Rosiglitazone and pioglitazone are the exogenous PPAR γ ligands which their anti-diabetic effects have been recognized.³⁸ In our pervious study rosiglitazone and pioglitazone administration also improved PTU-caused thyroid dysfunction through enhancing the serum level of T4 in the rats.²¹ According to the reports, PPAR γ ligands have been demonstrated to have fruitful impacts on the function of various systems including urinary system, cardiovascular system, respiratory system, and nervous system.^{31,39} In our study, administration of rosiglitazone and pioglitazone reduced the blood concentration of BUN and creatinine. These data indicate that these PPAR γ agonists could modify kidney dysfunction caused by hypothyroidism in rats. Furthermore, one of good effects of PPAR γ ligands is their ability in modulation of oxidative status.⁴⁰ The results of *in vitro* and *in vivo* studies

reveal that PPAR γ agonists stabilize the membrane of mitochondria and rescue the cells from apoptosis.⁴¹ Based on *in vitro* studies, PPAR γ agonists also attenuated the malic effects of oxidative stress via suppression of NADPH and NAD oxidases. Inhibition of caspase 3 and protection of liver tissue against cyclosporine-induced hepatotoxicity is also attributed to rosiglitazone.¹⁷ It has been documented that pioglitazone could improve the high blood pressure and renal oxidative injury in diet-triggered obesity in rats.⁴² Pioglitazone also protected cardiovascular system against oxidative stress resulting from metabolic syndrome in rats by modulating the level MDA and SOD.⁴³ According to the results of our study, pioglitazone and rosiglitazone decreased the accumulation of MDA and increased the concentration of total thiol and the activity of SOD and CAT in groups treated by these drugs compared with hypothyroidism group. Based on these results, we guess that the protective effect of pioglitazone and rosiglitazone against kidney dysfunction caused by hypothyroidism may be mediated through balancing the oxidative stress status. Additionally, PPAR γ ligands such as pioglitazone can exert their protective effects by disrupting the inflammatory mediators and preventing the cell apoptosis.^{44,45} Based on these findings, anti-inflammatory and antiapoptotic properties of rosiglitazone and pioglitazone also may be involved in their reno-protective impacts in current study. Therefore, more studies are required to determine the accurate mechanisms in future.

We also compared the effect of pioglitazone and rosiglitazone on kidney injury resulted from hypothyroidism. The results demonstrated that dose 4 mg/kg of rosiglitazone had a better reno-protective effect than dose 2 mg/kg of this drug and used doses of pioglitazone. PPAR γ has been understood to be very flexible and it has various patterns of ligand binding for different ligands. This finding shows that PPAR γ has the different affinity for its ligands.⁴⁶ Given this subject, better

effect of rosiglitazone than pioglitazone on kidney function that was seen in this study can be attributed to higher affinity this ligand to PPAR γ . However, it needs to be more explored in future. In summary, the findings of this study suggest that pioglitazone and rosiglitazone probably attenuated hyperthyroidism-caused kidney injuries by mitigating the oxidative stress. Although these findings prepare primarily evidence of reno-protective impact of pioglitazone and rosiglitazone, further evaluations such as molecular and histopathological studies are required to elucidate precise mechanisms. In addition, in this study we were constrained by budgetary in doing some tests including molecular and pathological assessments.

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Authors' Contribution

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Competing Interests

The authors declare no competition of interests.

Data Availability Statement

All findings are presented in this manuscript.

Ethical Approval

This pronged was carried out based on guidelines for working with laboratory animals approved by ethical committee (IR.MUMS.MEDICAL.REC.1399.304).

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Legend of figures

Figure 1: Comparison of blood concentration of BUN (A) and creatinine (B) between groups. Results are presented as mean $\pm$ SEM (n=7). ** P<0.01 and *** P<0.001 compared with control group. + P<0.05, ++ P<0.01, and +++ P<0.001 compared with PTU group, #P<0.05, ## P<0.01, and ### P<0.001 compared to other treatment groups.

Figure 2: Comparison of kidney tissue concentration of MDA (A) and total thiol groups (B) between groups. Results are presented as mean $\pm$ SEM (n=7). *** P<0.001 compared with control group. ++ P<0.01 and +++ P<0.001 compared with PTU group, #P<0.05, ## P<0.01, and ### P<0.001 compared to other treatment groups.

Figure 3: Comparison of the activity of SOD (A) and CAT (B) in kidney tissue between groups. Results are presented as mean $\pm$ SEM (n=7). * P<0.01 and *** P<0.001 compared with control group. ++ P<0.05 and +++ P<0.001 compared with PTU group, #P<0.05, ## P<0.01, and ### P<0.001 compared to other treatment groups.

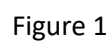


Figure 1

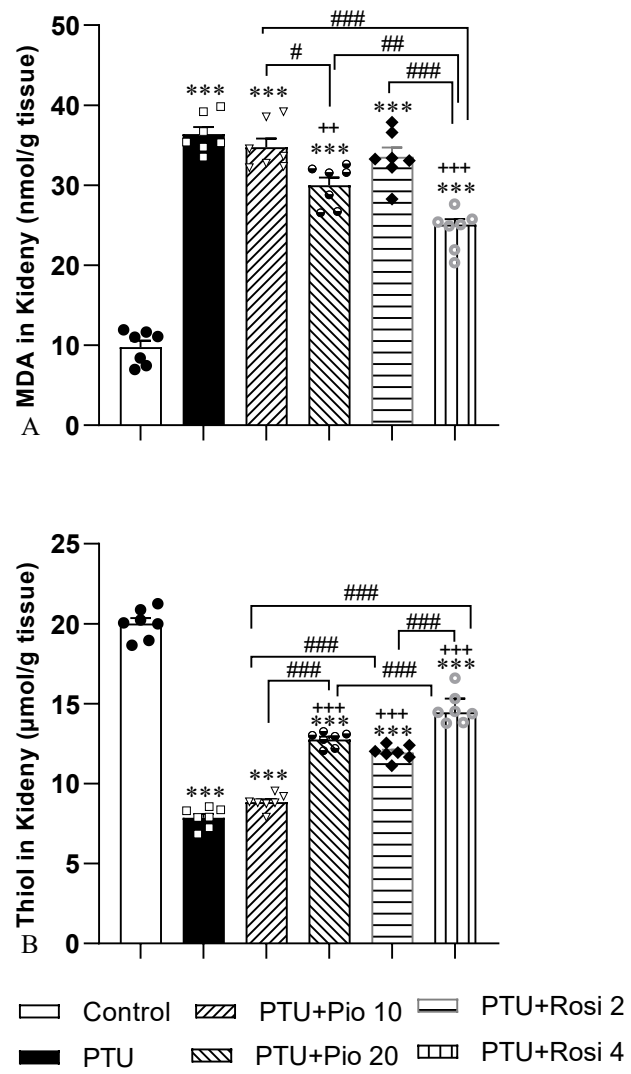


Figure 2

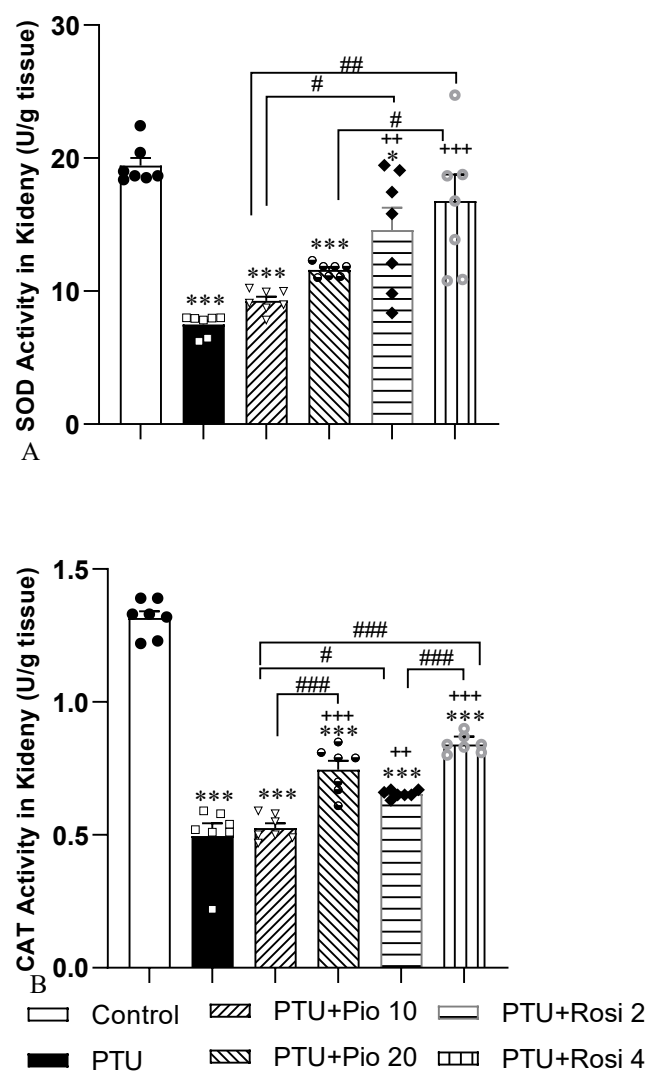


Figure 3